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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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DARBY & DARBY P.C.
P.O. BOX 770
Church Street Station
New York, NY 10008-0770

EXAMINER	
LEAVITT, MARIA GOMEZ	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,644	OHTA ET AL.	
	Examiner	Art Unit	
	MARIA LEAVITT	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-11 and 13-16* is/are pending in the application.

4a) Of the above claim(s) *3-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2 and 13-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06-22-2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 06-22-2009 has been entered.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
2. Status of claims. Claims 2-11 and 13-16 are currently pending. Claims 2, 3, 5, 13, 14 and 16 have been amended; claim 1 has been canceled by Applicants' amendment filed on 06-22-2009. Claims 1 and 3-11 were previously withdrawn from further consideration by applicants amendment filed on 05-05-2008 pursuant to 37 CFR 1.142(b), as being drawn to nonelected invention pursuant to 37 CFR1.14(b), there being no allowable generic or linking claim.
3. The examiner acknowledges receiving the Declaration under 37 C.F.R. § 1.132 signed by Dr. Hidetaka Seo (The Seo Declaration therefrom).
4. Therefore, claims 2 and 13-16 are currently being examined to which the following grounds of rejection are applicable.

Response to arguments

Rejection/objections maintained in response to Applicants' arguments or amendments.

Claim Rejections - 35 USC § 103

To the extent that the phrase "homologous recombination at an antibody locus" is broadly but reasonably interpreted as V(D)J recombination, the following rejection applies. The examiner notes that amending the claims to recite gene conversion, hypermutation, and switch recombination would overcome the obviousness of the rejection as discussed in the following paragraphs.

Claims 2 and 15 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Sonoda et al., (2001, *Phi. Trans. R. Soc.* London, 2001, 11-117) in view of McMurry et al., (2000, Science 495-498) and further in view of Watson et al., (2001, Recombinant DNA, pp. 297-304).

Sonoda et al., teaches the use of chicken B-lymphocyte line DT40 for the production of diverse antibodies. Moreover, Sonoda et al., discloses that efficient homologous recombination is an intrinsic characteristic of primary chicken B lymphocytes (p.111, col. 2). Further, B-lymphocye line DT40 exhibit Ig conversion by nucleotide sequence blocks derived from V region pseudogenes that are transferred to functional rearranged V(D)J segments. Indeed, refereeing to HR in DT40 cells, Sonoda states: "Although the presence of mismatches between the homologous substrate DNAs strongly suppresses HR reactions, divergence of sequences between the V region pseudogenes and the rearranged V gene does not appear to interfere with intragenic HR" (p. 111, col. 2).These teachings clearly indicate that B-lymphocyte line DT40 undergo earlier rearrangement of V(D)J segments in the chicken Ig loci by homologous recombination which is followed by gene conversion to generate diversity (p. 111, col.2).

Sonoda et al., does not specifically teach enhancing homologous recombination by relaxing the chromatin.

However, at the time the invention was made, McMurry et al., discloses a role for histone acetylation in the developmental regulation of V(D)J recombination. Specifically, McMurry et al., discloses that diversity in the V(D)J rearrangement of the T cell receptor depends on accessibility of said V(D)J locus to the recombinase activating enzyme (p. 495, col. 1 and 2). Moreover, McMurry et al., teaches a model for V(D)J recombination by inducing the region- and developmental stage-specific hyperacetylation of histone H3 which directs accessibility of recombinase enzymes to the V(D)J locus (p. 497, col. 2, last paragraph).

Sonoda and McMurry et al., do not specifically disclose that regulation of V(D)J recombination is the same in T cells and immunocytes producing antibodies.

However, at the time the invention was made it was well known in the art as exemplified by the teachings of Watson that recombination of the V, D, J and C segments in T cell receptor genes is similar to the recombination of the antibody V(D)J genes (pp. 303-304).

Therefore, in view of the benefits of using a B-lymphocyte line DT40 for the production of diverse antibodies which exhibit earlier rearrangement of V(D)J segments by HR as taught by Sonoda, it would have been *prima facie* obvious for one of skill in the art to enhance accessibility of the recombinant activating enzyme to the V(D)J locus by relaxing the chromatin structure of chromosomes in the DT40 B-lymphocytes , particularly because McMurry demonstrates that regions displaying H3 hyperacetylation facilitate direct access of recombinase enzymes to the in the TCR gene for V(D)J recombination reaction. Moreover, it would have been *prima facie* obvious for one of skill in the art that if acetylation of histone provides accessibility of recombinase activating enzyme to the V(D)J locus in a T cell, it would also provide accessibility to the recombinant enzyme to earlier rearrangement of V(D)J segments by

HR at the antibody locus in chicken-derived B cells, as the molecular bases of homologous recombination generating genetic diversity for the V(D)J locus are similar in both T and B cells. The manipulation of previously identified DNA fragments and cell transformation systems is within the ordinary level of skill in the art of molecular biology. One of ordinary skill in the art at the time the invention was made would had been motivated to combine the Sonoda, McMurry and Watson references with a reasonable expectation of success, particularly to improve the production of antibodies by homologous recombination by allowing accessibility of recombinant enzymes to regulate V(D)J recombination.

Response to Applicants' arguments as they relate to rejection of claims 2 and 15 under 35 USC § 103

At pages 7-13 of the remarks filed on 06-22-2009, Applicants essentially argue that: 1) V(D)J recombination reaction and homologous recombination (in the gene conversion method of the present invention) are different mechanisms, in part because, V(D)J recombination requires "site-specific endonucleases", called RAG1-RAG2, which mediate double –strand break repair by homologous recombination whereas gene conversion requires activation induced cytidine deaminase (AID) as evidenced in paragraphs 9, 10, 11, 13 and 14 of the Seo Declaration, 2) differences between homologous recombination and V(D)J recombination are highlighted at Table 1, at page 9 of remarks, summarizing important differences disclosed in paragraphs 8-14 of the the Seo Declaration, 3) the mechanism of gene conversion (of which homologous recombination is a species) was not elucidated at the relevant time and specially the mechanism of AID was unknown (the effective filing priority of the instant invention is July 30, 2002), 4) regardless of the mechanism of AID, the effect of trichostatin A (TSA) in cells undergoing gene

conversion, i.e. whether TSA activated or inactivated homologous recombination was unpredictable and 5) the reference of Agata et al., (2001, J. Exp. Med. pp873-879) insofar as how TSA induces chromatin accessibility for developmental rearrangement in T cell receptor cannot provide a basis for a reasonable expectation of success with the teachings of McMurry et al., (2000, Science 495-498) essentially because McMurry et al., teaches that hyperacetylation would be beneficial in V(D)J recombination whereas TSA in Agata has little effect on active V gene loci. While homologous recombination requires V gene loci that are already active, Agata, only observes a mild increase of several percent in V(D)J recombination events. Moreover, McMurry does not teach a histone deacetylase inhibitor. Thus, Applicants allege the findings of Agata establish why a skilled artisan would not have had a reasonable expectation that "hyperacetylation, as McMurry teaches for V(D)J, would be beneficial in the gene conversion (homologous recombination) context of the present invention". The above arguments have been fully considered but deemed unpersuasive.

Regarding 1), the fact that RAG is functional only in V(D)J recombination at the Ig locus by a single homologous recombinant event due to rearrangement of antibody light chain genes, i.e., a single V to a single J, or rearrangement of the heavy chain genes i.e., a single D to a single J and then a single V to the fused D-J segment, generating a functional VJ or VDJ product, which is different to the mechanism of AID, active in gene conversion in chickens (e.g., possessing only one functional V region), where diversification of the V region is accomplished by successive homologous recombination with upstream pseudo genes that transfers blocks derived from V regions pseudo genes to rearranged VJ segments is not disputed (See, Arakawa, 2004, Developmental Dynamics, pp. 458-464; page 460, Fig. 2, legend). However, at the

effective time of filing, the mechanism of homologous recombination in chicken-derived B cells was known in the art to encompass two processes: high targeting efficiency of exogenous DNA into the genome by intrinsic homologous recombination (HR) and intrachromosomal Ig gene conversion wherein nucleotide sequence blocks derived from V region pseudogenes are transferred into the functional rearranged V gene as evidenced by Sonoda et al., (p. 111, col. 2). Hence, enhancing homologous recombination at an antibody locus as claimed broadly read on V(D)J recombination and gene conversion in chicken-derived B cells. Likewise, at the effective time of filing, Arakawa et al., (Science. 2002 pp. 1301-6) discloses that chicken derived B cells first assemble their antigen receptor genes from different V, D and J segments by site specific V(D)J recombination, then, B cells further modify the rearranged V segments by untemplated hypermutations or pseudogene templated gene conversion (p. 1301, col. 1 and 2). Indeed, Arakawa et al., discloses that the AID gene disruption in DT40 completely blocks Ig gene conversion (p. 1305, col. 1, last paragraph). Moreover, paragraph 11 of the Seo Declaration further confirms that the difference is between V(D)J recombination (carried out by ubiquitously expressed nonhomologous DNA joining end-proteins, the Seo Declaration paragraphs 10, 11, and 13) and gene conversion and not homologous recombination. (See also Bassing et al., 2002, for V(D)J recombination in both immunoglobulins (Ig) and T cell receptor in developing B and T lymphocytes, respectively).

Regarding 2), insofar as paragraph 9 of the Seo Declaration based on the teachings of Grawunder et al. (1998, Molecular Cell, 1998, pp. 477-484), the examiner notes the article clearly teaches at page 477, col. 1, paragraph 1, that there are two pathways to repair double-strand DNA breaks, homologous recombination (HR) and nonhomologous end joining (NHEJ).

However, the article does not disclose how V(D)J recombination correlates to homologous recombination (HR) or nonhomologous end joining (NHEJ). The publication merely teaches how the process of V(D)J recombination in a human B cell line relies on NHEJ proteins for the joining step, and furthermore, how abrogation of human ligase IV significantly reduces V(D)J recombination as part of the NHEJ joining step. Hence the article is irrelevant as to how double strand breaks during late S and G2 are solely related to homologous recombination and double strand breaks during late G0 and G1 are solely related to V(D)J recombination as highlighted in table 1. Both HR and NHEJ are essential on V(D)J recombination. There is not disclosure of how DNA breaks in the process of homologous recombination on a chicken B-cell line compares to V(D)J recombination reaction in other B-cell line. Indeed, post filing art of Arakawa (2004), provides further insight into the different mechanism of V(D)J recombination and gene conversion and not homologous recombination in chicken B-cell lines by describing that in the mechanism to generate antibody diversity recombinant enzymes RAG is critical on initiating V(D)J recombination and cytidine deaminase critical on gene conversion activity. The author describes that RAG initiates V(D)J recombination by introduction of DNA double-strand breaks (DSBs). Then, AID scans the rearranged V segments and induces a change in the DNA structure by catalyzing cytosine deamination leading to guanine/uracil mismatches (page 463, col. 1). The resulting single-stranded break could be the stating point for a recombination reaction involving a homologous pseudogene. Hence, the different mechanisms to generate a diversity of antibodies in chicken B-cell lines are based on initial V(D)J recombination followed by gene conversion, both procedures involve homologous recombination mechanisms. The examiner notes that

Applicants have used post filing art of Arakawa (2004) at paragraphs 12 and Table 1 to support their conclusions.

Regarding 3), at the effective time of filing, it was known that AID gene disruption in DT40 produces a complete block of Ig gene conversion (p. 1305, col. 1, last paragraph) and that the AID gene was homologue to the APOBEC-1 gene, e.g., having a cytidine deaminase activity similar to APOBEC-1 (p. 1303, col. 1) and essential for somatic hypermutation and class switch in the mouse (Muramatsu et al.,2000) and human (Revy et al., 2000; Dundley, 2002; Harris 2002). The examiner agrees with Applicants that at the effective time of filing there were two hypotheses for the mechanism of AID in gene conversion as evidenced by Arakawa (2004). However, the claims as written do not recite the limitation of "gene conversion".

Regarding 4), regarding Applicants' argument that, regardless of the mechanism of AID, the effect of trichostatin A (TSA) in cells undergoing gene conversion i.e. whether TSA activated or inactivated homologous recombination was unpredictable ", is not found persuasive because it is noted that the features upon which applicant relies (i.e., cells undergoing gene conversion) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). This is the case here. The claims do not recite cells undergoing gene conversion as taught in the specification (see Figure 3(a) gene conversion as one of the mechanism generating homologous recombination in addition to gene insertion, gene deletion, and point mutations). Hence the argument is not persuasive as they argue limitations that are not present in the claims.

Regarding 5), the Examiner strenuously disagree with Applicants' position that it would have been unobvious to a skilled artisan to treat B-lymphocytes exhibiting gene conversion as taught by Sonoda with a deacetylase inhibitor to enhance accessibility of the RAG protein as taught by McMurry in view of the teaching of Agata, based on the data illustrated at page 876, Table 2. The Examiner notes in Agata both the Vγ2 locus and Vγ3 locus are actively rearranging during fetal development at days 10 and 14 in the presence (+) and absence (-) of TSA (Figure 2B, Fetal liver) indicating that in both Vγ2 locus and Vγ3 locus recombination signal sequences (RSSs) recognized by RAG-1 and RAG-2 comprise high levels of acetylation (p. 876, col. 2, paragraph 1). In contrast, germline transcripts as well as rearrangements of Vγ3 dramatically decreased in adult TN thymocytes, whereas those of Vγ2 were still predominant (Figure 2B, Adult BM). Accordingly, TSA treatment, of Vγ3 but not Vγ2 increases locus recombination, indicating that that inhibition of histone deacetylation by TSA leads either to specific induction of Vγ3 recombination or to selective expansion of Vγ3-rearranged cells (p. 877, col. 1 paragraph 1). Conceivable, because level of acetylation at RSS remain elevated in adult derived cells at the Vγ2 locus, TSA would not be required because histone acetylation already makes accessible chromatin to recombinant RAG enzymes. In relation to the deacetylase inhibitor, TSA, inhibiting histone deacetylation, the examiner agrees that McMurry et al., merely teaches that developmental stage-specific hyperacetylation of histone H3 directs accessibility of recombinase enzymes to the V(D)J locus. However, it would have been *prima facie* obvious for one of skill in the art that if acetylation of histone provides accessibility of recombinase activating enzyme to the V(D)J locus in a T cell, preventing histone deacetylation leading to elevated levels of histone acetylation, hyperacetylation would reasonably be expected to facilitate chromatin access of

other recombinant enzymes in the process of V(D)J recombination in both immunoglobulins (Ig) and T cell receptor in developing B and T lymphocytes, respectively. Furthermore, Applicants' arguments are not persuasive as they rely on limitations, e.g., "that hyperacetylation, as McMurry teaches for V(D)J, would be beneficial in the gene conversion (homologous recombination) context of the present invention" that are not present in the claims as written.

Claims 13-14 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Sonoda et al., (2001, *Phi. Trans. R. Soc.* London, 2001, 11-117) in view of McMurry et al., (2000, Science 495-498) and further in view of Watson et al., (2001, Recombinant DNA, pp. 297-304) as applied to claims 2 and 15 above and further in view of Choy et al., (Mol Cell Biol. 2002, pp 8215-8225) .

Response to Applicants' arguments as they relate to rejection of claims 13 and 14 under 35 USC § 103

At page 14 of remarks, Applicants essentially argue that Choy teaches transcription of a gene thus one of ordinary skill in the art would not seek guidance from a reference related to a non-analogous art, e.g., gene transcription vs. enhancing homologous recombination. Such is not persuasive.

Choy et al., complements the teachings of Sonoda, McMurry and Watson by disclosing that transcription requires acetylation of histone N-terminal tails to promote an open chromatin conformation. Transcription of rearrange V(D)J DNA follows V(D)J recombination, thus one of ordinary skill in the art would appreciate that by opening of the chromatin, selective expansion of V(D)J -rearranged cells is facilitated in the process of generating a diversity of antibodies as

claimed. Hence, if trichostatin A is a histone deacetylase inhibitor it should reasonably be expected to facilitate access to a recombinant enzyme in the V(D)J recombination in immunoglobulins (Ig) and to expand V(D)J -rearranged cells.

Claim 16 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Sonoda et al., (2001, *Phi. Trans. R. Soc.* London, 2001, 11-117) in view of McMurry et al., (2000, Science 495-498) and further in view of Watson et al., (2001, Recombinant DNA, pp. 297-304) as applied to claims 2 and 15 above and further in view of Sale et al., US Patent 7,122,339, Date of Patent October 17, 2006.

Response to Applicants' arguments as they relate to rejection of claim 16 under 35 USC § 103

At page 15 of remarks, Applicants essentially argue that Sale teaches a method for preparing an antibody-producing cell line capable of directed constitutive hypermutation of a specific nucleic acid region. Thus, one of ordinary skill in the art, when looking to design a method of enhancing homologous recombination during antibody production, would not seek guidance from a method for preparing an antibody producing cell line as taught by Sale. Such is not persuasive.

Applicants have not provided new arguments to rebut rejection of claim 16 under 35 U.S.C. 103(a) The Examiner refers Applicants to arguments as set forth in the paragraphs above and to the reasons of record, as disclosed in the previous office action of 07-25-2008 .

New grounds of objection/rejection

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 2 and 13-16 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that it fails to point out what is included or excluded by the claim language.

Claim 2 is vague and indefinite in its recitation of the phrase "enhancing DNA recombination at an antibody locus when producing antibodies from chicken-derived B cells in which DNA homologous recombination is occurring at the antibody locus". Likewise, claim 16, subpart i) is vague and indefinite in its recitation of the phrase "enhancing DNA recombination at an antibody locus when producing antibodies from chicken-derived B cells in which DNA homologous recombination is occurring at the antibody locus". The art at the time of filing exemplified by Sonoda et al., (2001, *Phi. Trans. R. Soc.* London, 2001, 11-117) discloses that homologous recombination using the chicken-derived B cells encompass two processes: high targeting efficiency of exogenous DNA into the genome by intrinsic homologous recombination (HR) and intrachromosomal Ig gene conversion wherein nucleotide sequence blocks derived from V region pseudogenes are transferred into the functional rearranged V gene (p. 111, col. 2). Similarly, Arakawa et al., (Science. 2002, pp. 1301-6) discloses that chicken derived B cells modify the rearranged V segments after site-specific V(D)J recombination by pseudogene template gene conversion and, in chicken B cell line DT40, disruption of the AID gene Ig gene abrogates Ig gene conversion in the Ig light chain. The specification as filed discloses in Figure

3(a) gene conversion as one of the mechanism generating homologous recombination in addition to gene insertion, gene deletion, and point mutations. Hence it is unclear whether enhancing DNA homologous recombination at an antibody locus refers to the mechanism of earlier site-specific V(D)J recombination or the following recombinant events of gene conversion in chicken-derived B cells, wherein stretches of nucleotide sequences from one of several pseudogene V elements are recombined into the VDJ exon to generate diversity. As the phrase "enhancing DNA recombination at an antibody locus" appears to be reciting separate process of homologous recombination that take place in chicken-derived B cells, its meaning and the metes and bounds of the claim as whole are unclear.

Claims 13-15 are indefinite insofar as they depend from claim 2.

For the purpose of a compact prosecution the phase "homologous recombination" has been interpreted as V(D)J recombination. Note that by amending the claims to recite gene conversion, hypermutation, and switch recombination, the obviousness of rejection of claims 2 and 13-16 under 35 USC § 103 would be overcome.

Conclusion

Claims 2 and 13-16 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/Maria Leavitt/
Maria Leavitt, PhD
Examiner, Art Unit 1633